in which one end was blocked by protein to mimic a double-stranded break. They observed an Sae2-dependent degradation product indicative of a nick internal to the protein-blocked DNA end. The researchers showed that this previously undocumented endonuclease activity was inherent to Mre11 — they repeated the experiment using a variant of the MRX complex containing a nuclease-defective version of Mre11, and observed no endonuclease activity.

Binding and hydrolysis of ATP molecules cause large conformational changes in the Rad50 subunit of the MRX complex, activating Mre11 nuclease activity[10,11]. Cannavo and Cejka observed MRX- and Sae2-dependent clipping activity only in the presence of ATP. This was eliminated using MRX mutants that were unable to bind or hydrolyse ATP. By adding protein blocks at both ends, the authors prevented the 3′–5′ exonuclease action of Mre11 and, using labelling techniques, they then mapped the site at which the enzyme clipped the DNA to around 15 to 20 nucleotides from the break ends. Thus, the properties of the *in vitro* reaction reported by Cannavo and Cejka match the known requirements for homologous recombination *in vivo*[2,3]. Furthermore, this study explains how Mre11 promotes resection of the 5′-terminated strand.

One key question is how Sae2 regulates MRX endonuclease activity. Phosphate molecules, which can modify protein behaviour, are added to Sae2 by a protein-kinase enzyme through phosphorylation when cells enter the S phase of the cell cycle. Mutation of a serine amino-acid residue (serine 267) to an alanine residue that cannot be phosphorylated severely impairs Sae2 function *in vivo*[12]. Cannavo and Cejka found that this mutant protein rendered MRX unable to clip double-stranded DNA. In addition, they showed that dephosphorylation of Sae2 with a phosphatase enzyme decreased its activity. These data suggest that Sae2 acts as a phosphorylation-dependent switch to trigger MRX endonuclease activity.

Because MRX clipping is dependent on ATP, and a specific point mutation in the *RAD50* gene, like loss of Sae2, prevents DNA clipping[13], it is likely that Sae2 acts through Rad50 to activate Mre11. Cannavo and Cejka detected a physical interaction between Sae2 and MRX, but found that, instead of the anticipated interaction with Rad50, only the Mre11 and Xrs2 subunits interacted with Sae2.

The CtIP protein is considered to be the equivalent of Sae2 in vertebrate cells and plays a crucial part in end resection. Two papers published earlier this year reported that CtIP has nuclease activity[14,15]. However, the protein's active site is not in its evolutionarily conserved carboxy-terminal domain, which, as the current study shows, is required in Sae2 to stimulate the latent MRX endonuclease. This raises the question of whether CtIP has further functions and can process DNA independently of the vertebrate form of MRX.

Cannavo and Cejka's study provides mechanistic insight into how MRX and Sae2 initiate end processing, but leads to more questions. For example, how does MRX recognize a protein-blocked end? How does a blocked end trigger cleavage of the 5′ strand? Finally, there is the question of how Sae2 phosphorylation coordinates with the ATPase activity of MRX to activate Mre11 endonuclease activity. ■

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SOLAR SYSTEM

Not just a storm in a teacup

The cloud that emerged above the south pole of Saturn's moon Titan in 2012 has been found to consist of hydrogen cyanide particles. This unexpected result prompts fresh thinking about the atmosphere of this satellite. SEE LETTER P.65

CAITLIN A. GRIFFITH

In May 2012, a large spinning cloud appeared over the southern pole of Saturn's moon Titan, where it persists still[1] (Fig. 1). The composition of the cloud has eluded identification until now. On page 65 of this issue, de Kok *et al.*[2] provide strong evidence for an unexpected answer: the cloud is made of hydrogen cyanide (HCN) ice particles. This result is difficult to refute because two spectral features indicate the presence of HCN, rather than of a HCN polymer[3], and the cloud's mass is consistent with that predicted for a cloud composed of HCN. The only problem is that the cloud, at an altitude of 300 kilometres, is not where it is supposed to be.

HCN is expected to condense in Titan's atmosphere at an altitude of 80 km; indeed, a nearly imperceptible tropical haze layer at this height matches the anticipated effects of HCN condensation[4]. By contrast, as discussed by de Kok and colleagues, the south polar HCN cloud emerged in the satellite's southern polar winter and resides in a region where, only three months earlier, the Cassini spacecraft's infrared spectrometer measured a temperature of 170 kelvin, which is 45 K too warm for HCN to condense[5].

The next temperature measurement by Cassini will occur in 2015. Perhaps these data will reveal that Titan's atmosphere is appropriately cool at an altitude of 300 km, arming theorists with enough information to understand the complex conditions of the polar winter. Barring this inconvenience with the temperature, HCN clouds at high polar altitudes can form by processes that are typical of Earth's atmosphere, a point that becomes apparent when considering the broader context of Titan's atmospheric chemistry and dynamics.

Titan's atmospheric composition resembles certain models of early Earth, before oxygen was a significant component of our atmosphere and when methane (CH_4) may have carried much of the atmospheric carbon[6]. Titan's two most abundant constituents, nitrogen (N_2) and methane, control the atmospheric make-up. These molecules are broken apart in the upper atmosphere (at roughly 1,000 km altitude) by solar ultraviolet radiation in a process called photolysis, thereby yielding reactive radicals, which initiate the production of complex organic molecules. The main nitrogen-containing molecule produced, HCN, regulates the production of nitrogen species.

The photochemically produced molecules mix down to the lower atmosphere while chemically mingling to form new molecules. Eventually, they settle on the moon's surface

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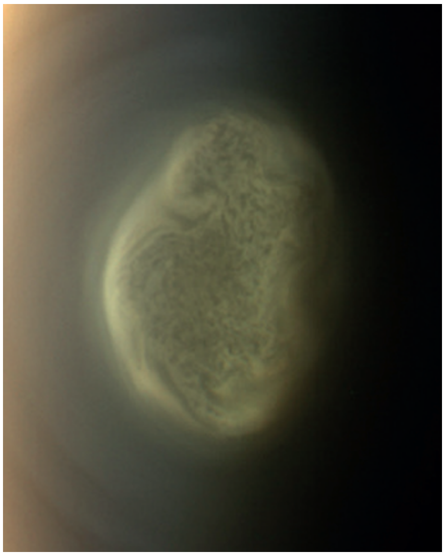

Figure 1 | Titan's south polar cloud. The cloud rises above the winter darkness of Titan's southern pole and catches the glint of sunlight. De Kok *et al.*[2] find that this spinning cloud, which completes an orbit in 9 hours — much faster than Titan's 15-day orbit — is composed of hydrogen cyanide. This orbital period signals the formation of a polar vortex as the southern pole enters into winter darkness[14]. The image, taken by the Cassini spacecraft's Imaging Subsystem, is centred near the south pole and extends over a distance of about 1,000 kilometres.

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in organic lakes and puddles, with a 'soup base' of methane and ethane (C_2H_6) that resembles natural gas[7,8]. As these nitrogen-bearing molecules diffuse downward, they are steered towards Titan's winter pole by atmospheric circulation[9]. Here they enter cooler regions and condense into clouds at different atmospheric layers, depending on their different thermodynamic properties.

Two distinct kinds of cloud cap the winter pole, both identified from measurements made by Cassini's Visual and Infrared Mapping Spectrometer: one at 55 km altitude, which is consistent with a C_2H_6 composition[10], and one at 300 km, found by de Kok and colleagues to be made of HCN. These stacked clouds, composed of the most abundant nitrogen and carbon photochemical species, track seasonally with the winter pole. An HCN cloud was previously identified[8] above Titan's north pole at the end of the northern winter, and the C_2H_6 cloud has vanished from this region in preparation for its southerly migration for the winter[11].

The winter pole on Titan is a peculiar place. Here the atmosphere radiatively cools during winter's darkness, triggering a suite of dynamical atmospheric responses. As discussed by de Kok and colleagues, the polar temperature is regulated by the intertwined effects of atmospheric chemistry, radiation and dynamics, which control the atmosphere's absorption and emission of radiation, and the compression, expansion and mixing of Titan's gases. A potential explanation for the polar HCN clouds is that they form from a process known as open-cell convection, in which cool, dense air sinks and warms slightly while the surrounding air rises and cools, thereby forming clouds (Fig. 1). The cool polar atmosphere also contrasts with the warmer lower latitudes. The resulting decrease in temperature with increasing latitude affects the atmosphere's pressure structure, which, when combined with Titan's spin, implies circumpolar winds that become more strongly westerly with altitude[12]. Titan's atmospheric polar vortex, witnessed by the rapid spin of the south polar HCN cloud, isolates the polar air from the rest of the atmosphere, allowing the pole to cool further. The presence of clouds spinning in a vortex can thus naturally emerge at a winter pole.

However, the detailed operations of Titan's winter pole, such as the seasonal evolution of the chemistry and temperature at 300 km altitude, are complicated and far from understood[12]. Better grasped is Earth's polar atmosphere, where the winter polar vortex is a repository of unique composition and clouds. The polar chemistry evolves from winter to spring with the production and loss of many molecular species that ultimately control the polar ozone abundances.

Laboratory simulations suggest that the photochemistry in Titan's atmosphere produces amino acids and nucleotide bases[13]. How far the chemistry evolves in Titan's upper atmosphere is unclear, and would probably require detailed *in situ* sampling of the upper atmosphere. However, further understanding of Titan's organic chemistry will entail studies of the abundance, phase and particulate composition of the main nitrogen photochemical product, which affects the overall nitrogen chemistry. The presence of an HCN maelstrom opens investigations into a new avenue of planetary-satellite organic chemistry — that of a cold and dark polar vortex stocked with nitrogen and methane photolysis products, which are typical of Titan and, perhaps, of early Earth. ■

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MEDICAL RESEARCH

Ebola therapy protects severely ill monkeys

A blend of three monoclonal antibodies has completely protected monkeys against a lethal dose of Ebola virus. Unlike other post-infection therapies, the treatment works even at advanced stages of the disease. **SEE ARTICLE P.47**

THOMAS W. GEISBERT

The filoviruses known as Ebola virus and Marburg virus are among the most deadly of pathogens, with fatality rates of up to 90% (ref. 1). Early this year, a new strain of the Zaire species of Ebola virus emerged[2] in the West African country of Guinea and quickly spread to Liberia, Sierra Leone and Nigeria. The outbreak persists despite the best efforts of local and international authorities, and is now the largest filovirus outbreak on record, with no end in sight. There are no licensed vaccines or post-exposure treatments against Ebola, so moving the most promising interventions forward is a matter of utmost urgency. On page 47 of this issue, Qiu *et al.*[3] report that rhesus monkeys can be completely protected from lethal Ebola infection using ZMapp — a blend of three monoclonal antibodies. Crucially, the treatment protected monkeys even when it was administered as late as 5 days after exposure to the virus, at a time when the animals were severely ill.

Since the discovery of Ebola virus (Fig. 1) in 1976, researchers have been actively developing treatments to combat infection. Studies

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